

Johns Hopkins University

**CLINICAL RESEARCH STAKEHOLDER PERCEPTIONS
OF PROTECTORS AGAINST MISCONDUCT:
DEVELOPING A SPONSOR QUALIFICATION TOOL**

by
CAROLINA MANCHOLA-OROZCO

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Abstract

The clinical research industry involves multiple entities working to provide evidence that hopes to bring new treatments that benefit the general public. Each entity has their respective goals to navigate and contributions to ensure that research subjects are safe during their participation in clinical trials. In the history of clinical research, there have been reports of research misconduct, where the interests of the participants were not of the utmost priority. The government has created new regulations and institutions have implemented procedures to ensure that risks of misconduct are mitigated.

The author examined the connection between stakeholders involved in the clinical research enterprise, and their respective roles and goals. These stakeholders include the sponsor, contract research organizations, principal investigators, and the research institution. At the center of the complementary entities are the patients that put their trust in the clinical research system to give themselves hope and contribute to and advocate for clinical research. Adult oncology Principal Investigators, Leaders, and Research Staff at the author's community hospital research practice graciously contributed to the conduct of this Capstone Project by completing a questionnaire assessing their needs and perceptions. There were areas identified for further investment within the institution's clinical research infrastructure. The author offered operational enhancements for the institution to implement and created a Sponsor Qualification Tool that will empower clinical research sites to determine if a sponsor and CRO are suitable for a productive and symbiotic partnership.

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Abbreviations

ACRP	Association of Clinical Research Professionals
CFR	Code of Federal Regulations
BCC	Blind Carbon Copy
CORO	Corporate Office of Research Operations
CRA	Clinical Research Associate
CRC	Clinical Research Coordinator
CRO	Contract Research Organization
FCA	False Claims Act
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
NDA	New Drug Application
PHI	Protected Health Information
PI	Principal Investigator
RIO	Research Integrity Officer
RVU	Relative Value Units
SD	Standard Deviation
USC	United States Code

Glossary

Informed Consent. According to the Food and Drug Administration, “the informed consent process involves three key features: (1) disclosing to potential research subjects information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research. Informed consent must be legally effective and prospectively obtained.”¹

Relative Value Units. “Medicare uses a physician fee schedule to determine payments for over 7,500 physician services. The fee for each service depends on its relative value units (RVUs), which rank on a common scale the resources used to provide each service. These resources include the physician’s work, the expenses of the physician’s practice, and professional liability insurance.”²

Research Misconduct. The Office of Research Integrity of the Department of Health & Human Services defines research misconduct as “fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results”³

Standard Deviation. Standard deviation in statistics, typically denoted by σ , is a measure of variation or dispersion (refers to a distribution's extent of stretching or squeezing) between values in a set of data. The lower the standard deviation, the closer the data points tend to be to the mean (or expected value), μ . Conversely, a higher standard deviation indicates a wider range of values.⁴

1. Informed Consent FAQs, Office for Human Research Protections, Department of Health and Human Services, accessed October 11, 2020, <https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html>

2. “Relative Value Units (RVUs)”. National Health Policy Forum, January 12, 2015, https://www.nhpf.org/library/the-basics/Basics_RVUs_01-12-15.pdf

3. “Definitions of Research Misconduct”. Office of Research Integrity, accessed October 4, 2020, <https://ori.hhs.gov/definition-research-misconduct>

4. Standard Deviation Calculator. accessed November 9, 2020, <https://www.calculator.net/standard-deviation-calculator.html>

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Chapter 1. Introduction

1.1. Background.

Clinical research is “research in which people, or data or samples of tissue from people, are studied to understand health and disease. Clinical research helps find new and better ways to detect, diagnose, treat, and prevent disease.”¹ A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.”²

Clinical Research Sites, Sponsor, and Contract Research Organizations (CROs) each have their role to fulfill within the clinical research enterprise. A research site is an institution where Human Subjects research is conducted.³ Research sites recruit patients and maintain certain quality measures to ensure that the patients are safe throughout their participation. A sponsor is the organization or investigator “who initiated the study and who has authority and control over the study.”⁴ A CRO is “a company hired by another company or research center to take over certain parts of running a clinical trial. The company may design, manage, and monitor the trial, and analyze the results.”⁵ Clinical research has many different players and phases of a project, and all of the stakeholders must trust each other and communicate their needs throughout the research process.

1. NCI Dictionaries, s.v. “Clinical Research,” accessed September 28, 2020, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/clinical-research>

2. 45 CFR 46.102

3. Ibid.

3. Glossary of Common Site Terms, s.v. “Sponsor,” accessed September 18, 2020, <https://clinicaltrials.gov/ct2/about-studies/glossary>

4. NCI Dictionaries, s.v. “Contract Research Organization,” accessed September 18, 2020, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/contract-research-organization>

5. Ibid.

1.2. Statement of the Problem.

These stakeholders have a duty to function together to push Investigational New Drugs (IND) to the marketplace, and to benefit patients with new effective treatments against such diseases as cancer. These same goals can also cause an unbalance within the separate entities, creating the potential for research misconduct if there is nothing to preempt fabrication (“making up data or results and recording or reporting them”)⁶, falsification (“manipulating research materials...or changing or omitting data or results such that the research is not accurately presented in the research record”)⁷, or plagiarism (appropriation of another person’s ideas, processes, results, or words without giving proper credit”)⁸ in clinical research conduct and reporting.

1.3. Project Question.

Due to the increasingly complex operational structure of clinical research and the multitude of risks that each stakeholder navigates, what are the perceptions of site investigators and staff, and how do they navigate these risks? What are the mitigating factors that protect principal investigators (PIs), research sites, sponsors and CROs from conducting misconduct in the course of their research? How do PIs, research site leaders and staff feel about their operations, and their interactions with sponsors and Contract Research Organizations? How can a research site standardize communicating their expectations to the external partners prior to study initiation? These are some of the questions the author of this Capstone Project will be addressing.

6. “Definitions of Research Misconduct”. Office of Research Integrity, accessed October 4, 2020, <https://ori.hhs.gov/definition-research-misconduct>

7. Ibid.

8. Ibid.

1.4. Project Objectives.

The author aims to examine goals and expectations from principal investigators, a research site, sponsors, and Contract Research Organizations and provide evidence to show that when the respective goals become unbalanced, the risk of costly research misconduct has an opportunity to flourish. The status of these relationships has the potential to benefit a patient when respective goals are communicated, and potentially harm the research patient population without transparency among all of the entities involved. In Figure 1. Relationships between clinical research stakeholders, there is a connection between the study sponsor, the CRO, the research site that recruits patients, and the PI that oversees the responsible conduct of research. The research patient is at the center of all of these processes and efforts to maintain integrity and quality. Patients are the entities the research enterprise seeks to benefit.



Figure 1. Relationships Between Clinical Research Stakeholders⁹

9. Naren R Ramakrishna, in collaboration with the author, September 18, 2020.

Research participants in this Capstone project will be given an opportunity to report their own perceptions on the research site's operations, and how effective they feel their relationship is with sponsors and CROs.

1.5. Significance.

There is currently sparse data examining the perceptions of clinical research practitioners in community oncology research regarding their internal practices and their relationships with Sponsors and Contract Research Organizations. This investigation will provide insight into the comprehensive interplay between the stakeholders, and how each stakeholder is responsible for their own conduct and monitoring others'. Historically, sponsors and CROs conduct unidirectional Site Qualification Visits to assess a potential research site's ability to conduct their trial. The author will develop a tool for sites to use to vet the Sponsor's and CRO's ability to support the site during the conduct of the trial.

1.6. Exclusions and Limitations.

For the purposes of this Capstone Project, the scope of the project includes data from clinical research stakeholders from a community hospital with an oncology department that currently runs over 170 clinical research studies. A questionnaire inquiring about clinical research goals and expectations was distributed to internal employees within an Adult Oncology practice. The clinical research stakeholders include principal investigators, research staff comprising of clinical research coordinators, regulatory coordinators, and data management staff, and leaders from the adult oncology and compliance divisions. The hospital contains a research compliance office with its own Institutional Review Board. The questionnaire was not distributed to

representatives of sponsors or Contract Research Organizations, so these opinions and perceptions are not present in the author's analysis. Collection of this important data is a limitation of this project. Further research is needed to seek the perceptions of agents from Sponsors and CROs to understand how they perceive their relationships among themselves and research sites, and how these interactions can protect against research misconduct.

Chapter 2. Literature Review

2.1. Overview of Literature Review.

The literature reviewed for this project includes the Code of Federal Regulations, the False Claims Act and The International Conference on Harmonization E6 Good Clinical Practice (ICH-GCP) guidance. The ICH-GCP was created to standardize research practice in the European Union, the United States, and Japan. These sources both govern and seek to mitigate the risks inherent in research conduct for all parties involved in human subjects research. All stakeholders in the research enterprise are required to have working knowledge of the regulations and guidance documents and receive periodic training to ensure compliance.

There is a limited amount of literature examining the role of Contract Research Organizations and their interactions with Sponsors and clinical research sites where human subjects research is conducted.

2.2. Details of Review.

2.2.1. Code of Federal Regulations.

The Code of Federal Regulations (CFR) are housed within the Federal Register of the United States government. Several of these CFR are central tenets to the practice of clinical research and protections for clinical research subjects. Title 21 Food and Drugs, Chapter 1 Food and Drug Administration, Department of Health and Human Services, Subchapter A General, Part 50 Protection of Human Subjects defines a “clinical investigation [as] any experiment that involves a test article and one or more human subjects.”¹⁰ An investigator is “an individual who actually conducts a clinical

¹⁰. 21 CFR 50

investigation, i.e. under whose immediate direction the test article is administered or dispensed to, or used involving, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.”¹¹ The team may consist of sub-investigators, clinical research coordinators, data management personnel, and regulatory support staff. A “human subject means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.”¹² This CFR is particularly important due to the Informed Consent requirements that are written. It details elements that informed consent must contain, and what provisions exist when informed consent is not feasible and an investigational product must be implemented. 21 CFR 50 also contains rules that Institutional Review Boards (IRBs) must follow. An IRB is a “board, committee, or other group formally designated by an institution to review biomedical research involving humans as subjects, to approve the initiation of and conduct periodic review of such research.”¹³

Another central CFR is Title 45 Public Welfare, Subtitle A Department of Health and Human Services, Subchapter A General Administration, Part 46 Protection of Human Subjects. 45 CFR 46 contains the Common Rule under Subpart A, Basic HHS Policy for Protection of Human Research Subjects.¹⁴ This describes the types of research that do not fall under the coverage of the policy. There is also a list of research activities that would not require informed consent. For the purposes of clinical research that tests investigational products on humans, the policy does apply. 45 CFR 46

11. 21 CFR 50

12. Ibid.

13. Ibid.

14. 45 CFR 46

describes the structure of an IRB and how they must operate and review different categories of research under the regulations. Informed consent is also covered under this regulation, so the gravity of proper informed consent is apparent to investigators. 45 CFR 46 also provides policies for involvement of vulnerable populations in clinical research. These include research involving pregnant women or fetuses, neonates, prisoners, and children. These regulations are to ensure that these participants are greatly protected and that no coercion occurs as a result of their vulnerable status.

2.2.2. The False Claims Act.

The False Claims Act (FCA) “was enacted in 1863 by a Congress concerned that suppliers of goods to the Union Army during the Civil War were defrauding the Army. The FCA provided that any person who knowingly submitted false claims to the government was liable for double the government’s damages plus a penalty.”¹⁵ Since its inception there have been changes to the Act increasing the damages and penalties that violators must pay.¹⁶ The liability under FCA applies to “any person who knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval; [or] knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent”.¹⁷ Per the US Code a person who knowingly commits applicable activities is one that “has actual knowledge of the information; acts in deliberate ignorance of the truth or falsity of the information; or acts in reckless disregard of the truth or falsity of the information; and require no proof of specific intent to defraud.”¹⁸

15 False Claims Act, 31 U.S.C. §§ 3729 – 3733, accessed September 30, 2020, https://www.justice.gov/sites/default/files/civil/legacy/2011/04/22/C-FRAUDS_FCA_Primer.pdf

16. Ibid.

17. False Claims, False Claims Act, 31 U.S.C. §§ 3729(a)(1)(A-B), accessed September 30, 2020, https://www.justice.gov/sites/default/files/civil/legacy/2011/04/22/C-FRAUDS_FCA_Primer.pdf

18. False Claims, False Claims Act, 31 U.S.C. §§ 3729(b)(1), accessed September 30, 2020, https://www.justice.gov/sites/default/files/civil/legacy/2011/04/22/C-FRAUDS_FCA_Primer.pdf

In clinical research, the ramifications of false claims are widespread and severe; fraudulent publications may arise and the public may be exposed to potentially harmful substances that have not been proven to be effective and safe.

2.2.3. ICH-GCP.

The Good Clinical Practice guidance was created under international collaboration between the European Union, the United States, and Japan to guide clinical research conduct to conform to a standard practice for “designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of trial subjects are protected...and that the clinical trial data are credible.”¹⁹ The new addendum E6(R2) is a comprehensive document that contains guidance for investigators, research sites, monitors, and sponsors.²⁰ While the recommendations in the document are not codified into the federal regulations, the suggestions presented are a beacon of practices that the Food and Drug Administration within the Department of Health and Human Services provides as a reference document for clinical research practitioners.

2.2.4. Contract Research Organization.

A Contract Research Organization (CRO) is “a company hired by another company or research center to take over certain parts of running a clinical trial. The company may design, manage, and monitor the trial, and analyze the results.”²¹

According to Roberts, Kantarjian and Steensma, “high-quality CROs have the potential

19. GUIDANCE DOCUMENT E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). 2018. Retrieved from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e6r2-good-clinical-practice-integrated-addendum-ich-e6r1>

20. E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1). FDA (2018). <https://www.fda.gov/media/93884/download>

21. NCI Dictionaries, s.v. “Contract Research Organization,” accessed September 18, 2020, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/contract-research-organization>

to add substantial benefit to the clinical trial process, including improving the quality of data collection and trial standardization.”²² CROs were initially created to meet an increasing need from the National Cancer Institute and pharmaceutical companies. They “were searching for ways to address rising research and development costs, including detailed required for New Drug Application submission to regulatory agencies such as US Food and Drug Administration (FDA)...CRO outsourcing provided ‘spillover capacity’ for data management and biostatistical analysis during peak activity periods, when the pharmaceutical companies’ own employees had insufficient capacity to complete all necessary tasks.”²³ Due to this delegation of operations to a third party, there is a “question whether CROs as currently constituted add an unnecessary layer of complexity to a clinical trial process already burdened by bureaucracy.”²⁴ Another issue within CROs is the attrition rate among their monitors. “The frequent high turnover rate [is] noted for monitors (due to their relatively low pay and often-cited desire to be hired by a pharmaceutical company because such companies usually provide greater upward mobility and employee benefits than CROs).”²⁵

2.2.5. Research Misconduct.

2.2.5.1. Issues with Informed Consent.

In the all-too recent history of clinical research, there have been egregious errors in the collection of informed consent. Informed consent ensures that the research subject fully understands the nature of the research, and that they agree to be subject to unapproved interventions. As is well-known in clinical research lineage, the Public

22. Daniel A. Roberts, Hagop M. Kantarjan, and David P. Steensma. “Contract Research Organizations in Oncology Clinical Research: Challenges and Opportunities”. *Cancer*, no. 122 (March 2016): 1476-82. <https://doi.org/10.1002/cncr.29994>

23. *Ibid.*

24. *Ibid.*

25. *Ibid.*

Health Service operated the Tuskegee experiments in which African American men who were infected with syphilis were denied standard treatment in order to study the natural history of the disease. The “men had agreed freely to be examined and treated. However, there was no evidence that researchers had informed them of the study or its real purpose. In fact, the men had been misled and had not been given all the facts required to provide informed consent.”²⁶ Subjects were never given an opportunity to decline participation or withdraw from the study. The study was initiated in 1932 and did not end until 1970 after serious ethical issues with the study were uncovered.²⁷

The Nazi in Germany conducted many horrific experiments on their prisoners. “Scientists there also carried out so-called freezing experiments on prisoners to find an effective treatment for hypothermia. Prisoners were also used to test various methods of making seawater drinkable.”²⁸ Josef Mengele infamously conducted research on twins. These Nazi studies eventually gave rise to the Nuremberg Code to ensure studies were completed only under the supervision of a qualified physician and that informed consent be administered to every research subject.

2.2.5.2. Investigator Research Misconduct.

There are many examples of research misconduct arising from investigators falsifying or fabricating data or demonstrating egregious conflicts of interest. Below is a small sample of publicly available notices of research misconduct that have been prosecuted for diverse reasons.

26. “The Tuskegee Timeline,” Centers for Disease Control, US Public Health Service Study at Tuskegee. Last modified March 02, 2020, <https://www.cdc.gov/tuskegee/timeline.htm>

27. Ibid.

28. “Nazi Medical Experiments,” Holocaust Encyclopedia, United State Holocaust Memorial Museum. Last modified August 30, 2006, <https://encyclopedia.ushmm.org/content/en/article/nazi-medical-experiments>

James Lieber from the University of California at Los Angeles,

knowingly and intentionally falsified and fabricated follow-up interview, urine samples, and urine sample records of human subject study participants and entered such false and fabricated data into the study's data base...the respondent fabricated interviews for 20 of the 53 interviews assigned to him...Aggravating factors included theft of \$5180 for incentive payments to subjects and travel expenses.²⁹

The Office of Research Integrity ultimately prohibited Mr. Leiber from “contracting or subcontracting with any agency of the United States government”³⁰ for a period of 3 years after the notice.

Dr. Charles Nemeroff, previously a psychiatry chairman at Emory University, had failed to disclose earnings from GlaxoSmithKline for touting their drug Paxil to physicians, while managing “a multi-million dollar grant from the NIH to research drugs under development by Glaxo.”³¹ He had also told Emory that “he would earn less than \$10,000 a year from GlaxoSmithKline to comply with Federal rules”, but would go on to earn nearly \$200,000, leading to an investigation by a United States Senator and departure from Emory. In 2009, “while negotiating with [University of Miami] for a job, Nemeroff even dangled the possibility of a new funder for the school if he was hired.”³² In the years since his chairmanship at the Department of Psychiatry at the University of Miami, he is currently chairman for the same at another academic institution.

Dr. Piero Anversa, former lab director from Harvard Medical School and Brigham and Women's Hospital, ran cardiac stem cell studies and allegedly falsified and/or fabricated data. “The hospital agreed to a \$10 million settlement with the U.S.

29. “Findings of research misconduct, PMC4259688.” NIH Guide for Grants and Contracts. Accessed October 23, 2020, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4259688/>

30. Ibid.

31. Paul Thacker, “How an Ethically Challenged Researcher Found a Home at the University of Miami,” Forbes, September 13, 2011, <https://www.forbes.com/sites/paulthacker/2011/09/13/how-an-ethically-challenged-researcher-found-a-home-at-the-university-of-miami/#5aaadbbe5e12>

32. Ibid.

government over allegations Anversa and two colleagues' work had been used to fraudulently obtain federal funding."³³ Harvard and Brigham and Women's Hospital have asked that Anversa's work "be retracted from medical journals."³⁴ Anversa's total number of retractions "would put him in the top 20 list of scientists with the most retractions in the world."³⁵ The article by Oransky and Marcus consider the ramifications to the scientific community at large, specifically what happens now "to work that was based on his work."³⁶

In October 2020, the Department of Justice (DOJ) published a notice regarding Sami Anwar of Washington state. Anwar was sentenced "to a 340 month term of imprisonment for falsifying human clinical research trials in connection with a fraud scheme"³⁷ he directed. "He was found guilty of 47 counts of wire fraud, mail fraud, conspiracy, fraudulently obtaining controlled substances, and furnishing false material information to the Drug Enforcement Administration."³⁸ He falsified research data on many different drugs tested for a large number of indications, and "the evidence at trial indicated that [he] and his companies received over \$5.6 million dollars from the fraud."³⁹ The following excerpt from the DOJ details systemic violations of patient trust, data manipulation, and employee harassment.

33. Ivan Oransky, and Adam Marcus, "Harvard and Brigham call for more than 30 retractions of cardiac stem cell research," Stat, October 14, 2018, <https://www.statnews.com/2018/10/14/harvard-brigham-retractions-stem-cell/>

34. Ibid.

35. Ibid.

36. Ibid.

37. "Richland Business Owner Sentenced to More Than 28 Years in Federal Prison for Falsifying Human Clinical Research Trials," United States Attorney's Office, Eastern District of Washington. United States Department of Justice, October 2, 2020, <https://www.justice.gov/usao-edwa/pr/richland-business-owner-sentenced-more-28-years-federal-prison-falsifying-human>

38. Ibid.

39. Ibid.

Sami Anwar, who is not a licensed medical doctor, would pose as a doctor and forge the signature of the doctors he employed. In addition, over a dozen former employees of Sami Anwar testified that he directly instructed them to assist him in committing the fraud including falsifying medical records and data to admit dozens of ineligible research subjects; falsifying research data including electrocardiograms and vital signs, obtaining blood specimens from Sami Anwar's employees or stealing them from unwitting medical patients of his medical center, disposing of study medications by shooting them down the drain and then falsely recording them as having been properly injected as required, dangerously hoarding opioids intended to be dispensed to study subjects, and fabricating required subject diary entries.

According to the evidence presented at trial and at sentencing [he] not only directed the fraud but engaged in threats, retaliation, and intimidation in order to hide his crimes from drug companies, the FDA, which regulated human clinical trials in the United States, and law enforcement.⁴⁰

This constitutes an extreme example of the violation of the principals of human subjects protections, which are enforced by multiple layers of oversight by investigators, Institutional Review Boards (IRB), clinical research associate monitors, and the sponsors themselves. At a minimum, clinical research studies are reviewed annually by an IRB to verify and ensure the safety of research subjects. Research monitors are sent by sponsors or contract research organizations (CROs) to periodically verify the accuracy of the data being collected and ensure that Good Clinical Practice guidelines are respected. With an extensive list of violations, the question of proper oversight remains.

40. "Richland Business Owner Sentenced to More Than 28 Years in Federal Prison for Falsifying Human Clinical Research Trials," United States Attorney's Office, Eastern District of Washington. United States Department of Justice, October 2, 2020, <https://www.justice.gov/usao-edwa/pr/richland-business-owner-sentenced-more-28-years-federal-prison-falsifying->

2.2.5.3. Sponsor Misconduct.

Pharmaceutical company GlaxoSmithKline (GSK), in *The United States v.*

GlaxoSmithKline lawsuit:

Agreed to plead guilty and to pay \$3 billion to resolve its criminal and civil liability arising from the company's unlawful promotion of certain prescription drugs, its failure to report certain safety data, and its civil liability for alleged false price reporting practices...GSK agreed to plead guilty to a three-count criminal information, including two counts of introducing misbranded drugs, Paxil and Wellbutrin, into interstate commerce and one count of failing to report safety data about the drug Avandia to the Food and Drug Administration (FDA).⁴¹

In the absence of safety data GSK published an article "that misreported that a clinical trial of Paxil demonstrated efficacy in the treatment of depression in patients under age 18."⁴² The United States further accused GSK of sponsoring "dinner programs, lunch programs, spa programs, and similar activities to promote the use of Paxil in children and adolescents."⁴³ Also in violation of the False Claims Act, GSK promoted "asthma drug, Advair, for first-line therapy for mild asthma patients even though it was not approved or medically appropriate under these circumstances."⁴⁴ The U.S. also included "...allegations that GSK paid kickbacks to health care professionals to induce them to promote and prescribe these drugs as well as the drugs Imitrex, Lotronex, Flovent and Valtrex."⁴⁵ GSK also omitted detrimental cardiac safety data for its drug Avandia, according to the report.

41. Office of Public Affairs, "GlaxoSmithKline to Plead Guilty and Pay \$3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data," United States Department of Justice, July 2, 2012, <https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report>

42. Ibid.

43. Ibid.

44. Ibid.

45. Ibid.

In a notice published by the Department of Justice in 2013, Johnson & Johnson and subsidiary Janssen,

Allegedly promoted the antipsychotic drug [Risperdal] for use in children and individuals with mental disabilities... Nonetheless, one of Janssen's Key Base Business Goals was to grow and protect the drug's market share with child/adolescent patients. Janssen instructed its sales representatives to call on child psychiatrists...to market Risperdal as safe and effective for symptoms of various childhood disorders, such as attention deficit hyperactivity disorder, oppositional defiant disorders, obsessive-compulsive disorder and autism. Until late 2006, Risperdal was not approved for use in children for any purpose, and the FDA repeatedly warned the company against promoting it for use in children.⁴⁶

The DOJ report also details that they paid "kickbacks to physicians to prescribe Risperdal...[in] children, the elderly and those with developmental disabilities."⁴⁷

In the literature there are many other examples of misconduct from sponsors, but the cases above demonstrate those with some of the largest fines. The imprint of harm caused by these cases extends to vulnerable populations and represents a disregard for the protections regulations and GCP.

2.2.5.4. Contract Research Organization Misconduct.

There is little literature regarding CRO misconduct, though some examples can be found. Laura LaRosa, writing for the Association of Clinical Research Professionals (ACRP) describes one case, "where a CRA with 20 years of experience was doing her job properly in the field, only to have an in-house CRA with four years of experience try to make her change reports to fit the study protocol. The experienced CRA finally refused to sign the report."⁴⁸ In another example, "CRAs were consistently

46. Office of Public Affairs, "Johnson & Johnson to Pay More Than \$2.2 Billion to Resolve Criminal and Civil Investigations," United States Department of Justice, November 4, 2013, <https://www.justice.gov/opa/pr/johnson-johnson-pay-more-22-billion-resolve-criminal-and-civil-investigations>

47. Ibid.

48. Lauren LaRosa, "Is CRA Fraud Undermining Clinical Trial Integrity?," Association of Clinical Research Professionals, June 5, 2017, <https://acrpn.net.org/2017/06/05/cra-fraud-undermining-clinical-trial-integrity/>

backdating, then often misfiling, interim visit follow-up letters.”⁴⁹ These errors LaRosa says, “are probably generated by time pressures, internal political pressure to keep a study moving, and a lack of education and training.”⁵⁰

2.3. Applicability of Literature Review.

Investigators, research sites, sponsors and CROs all must follow regulations and laws to ensure patient safety and accurate data collection and reporting. There is an extensive history of human rights violations in clinical research. After these case histories of research misconduct, the government has taken steps to codify rules to enforce human subject protections, especially with populations that may be vulnerable to coercion or unable to decide for themselves whether to participate in a research study. Research institutions have initiated using training modules like the Collaborative Institutional Training Initiative (CITI) program to ensure their research staff is aware of the history of research, how to avoid misconduct, and consequences of non-compliance. The manner in which investigators and clinical research staff perceive and navigate the internal operational layers of research bureaucracy and their interactions with sponsors and CROs are further examined in this project. The project will also report on preventative measures that have been instituted at a federal and institutional level to protect against misconduct.

49. Lauren LaRosa, “Is CRA Fraud Undermining Clinical Trial Integrity?,” Association of Clinical Research Professionals, June 5, 2017, <https://acrpnet.org/2017/06/05/cra-fraud-undermining-clinical-trial-integrity/>

50. Ibid.

Chapter 3. Need(s) Assessment

3.1. Need(s) Assessment.

This Capstone Project is needed due to the lack of understanding how clinical research entities such as principal investigators, research sites, sponsors and Contract Research Organizations support a common goal of treating patients safely with new drugs, all while carrying their own long-term goals and expectations of the outcome of a project. These goals, if left un-checked, can lead to possible research misconduct. The main objective for principal investigators at research sites is to protect the patient, which may be at odds with the main objectives for the sponsor who is manufacturing the investigational product, and the CRO which is contracted to the sponsor. Expectations are clearly communicated by the sponsor and CROs to the research site, yet sites do not have a formal standardized mechanism to dictate their overall goals and expectations of Sponsor and CRO performance.

3.1.1 Assessment of Need

The author conducted informal discussions with various principal investigators to gather their thoughts on risks and challenges inherent in conducting research at their facility. The author noticed trends in their topics, which included risks to themselves as the ultimately responsible party, and risks to the institution. The author then considered how principal investigators have general expectations of CROs and sponsors, and questioned how these are communicated during the conduct of a trial.

Sponsors and CROs communicate their expectations of sites prior to initiating any research project, but the communication of site expectations is not reciprocal prior to accepting a sponsor's study. A standardized tool for sponsor qualification is in order for the site to be able to assess the ability of the sponsor to support the site.

3.2. Metrics.

No formal metrics were used to assess the need for this study.

3.3. Sources.

The author is a clinical research coordinator who had informal conversations with oncology research principal investigators (PIs) regarding their perception of risk in conducting clinical research. The author then discussed the need to examine general clinical research stakeholder relationships with a PI.

3.4. Committees.

The author has not created a committee for guidance on this Capstone Project. The author has conferred with a physician-scientist who is the Director of the Center for Proton Therapy, Co-Chair of the Brain and Spine Tumor Center at the institution, and principal investigator in oncology research. This doctor is the author's mentor on the Capstone Project.

3.5. Committee Role.

The role of the mentor has been to guide the author in connecting concepts of risk and research misconduct that clinical research stakeholders encounter. They encouraged the author to maintain focus on the relationships between the institutions and how these relationships interplay to benefit the research patient. The mentor also challenged the author to create guiding principles that serve as stewards for clinical research practitioners.

Chapter 4. Project Description

4.1. Discussion of project elements.

The Capstone Project is a multi-faceted endeavor combining human subjects regulations and guidance, examining the roles of clinical research stakeholders and how they all interact to serve the patient. Case studies of research misconduct conducted by principal investigators, sponsors and CROs are presented that represent unbalanced goals that do not value the patient as the central figure that they all serve.

4.1.1. Project Questionnaire.

This questionnaire assessed the perceptions of adult oncology clinical research principal investigators, department leaders, and research compliance office leaders and staff with regard to their relationships and experiences with sponsors and Contract Research Organizations. A questionnaire was administered to adult oncology leaders, principal investigators and adult oncology research staff from a community hospital that contains its own research compliance office and clinical research departments that focus on specific diseases including pediatric oncology, emergency medicine, pediatric cardiology, and orthopedics, among others. The questionnaire was submitted to and approved by the Johns Hopkins University Homewood Institutional Review Board (IRB), and the IRB at the author's place of employment.

4.1.2. Sponsor Qualification Tool Development.

Once the subject responses to the questionnaire had been analyzed for the elements that the site personnel reported, a tool was developed to facilitate the initial contact between research sites, the prospective study sponsor, and the CRO contracted to the sponsor. In the current pre-contract process, the sponsor conducts a Site

Qualification Visit with information that the site unilaterally must provide in order to prove their aptitude in conducting the research that the sponsor is offering. This tool provides the research site with qualifying information regarding the sponsor's and CRO's abilities to support the site during the conduct of the trial.

Chapter 5. Methodology

5.1. Methodology Overview.

The author conducted a literature review of the human subjects regulations that all practitioners of clinical research must abide by. These standards are the framework by which institutional policies are written, and government granting agencies, sponsors and Contract Research Organizations are held to. Good Clinical Practice, a guidance document put forth by the International Conference on Harmonization is followed for its intent to standardize clinical research processes. Case studies of research misconduct arising from investigators, sponsors, and CROs were examined for their impact on patient safety and the impact to the scientific community.

Prior to initiating a research partnership, sponsors ask potential clinical research sites for their qualifications, understandably to assess the feasibility of conducting a trial with minimal issues and risk to the outcome of the research they are proposing. The author has created a survey to assess a sponsor's experience with conducting trials, and the infrastructure they have to assist sites from initiation to completion of a clinical trial. The hope is that this assessment will inform the institution of risk they assume in relying on sponsor and CRO processes.

5.2. Project Design and Discussion.

Early in the development of the Capstone Project, the author planned to conduct a questionnaire with clinical research investigators at their institution. As directed in *The Complete Guide to Writing Questionnaires*⁵¹ the author conducted preliminary

51. David F Harris, *The Complete Guide to Writing Questionnaires: How to Get Better Information for Better Decisions* (Durham, NC: I&M Press, 2014), 18-20.

conversations with a small number of principal investigators (PI's) to determine what their concerns were regarding the risks inherent in research conduct. The PI's identified categories of risk: risk to the investigator, risk to the institution, and risk to the patient. This led the author to consider how clinical research stakeholders interact to accept and mitigate risk within the institution. Clinical research is conducted in partnership with sponsors and contract research organizations who are working with sponsors to oversee clinical trial operations. The author and Capstone Project mentor discussed the ongoing relationship between all of the entities, and how their efforts should ultimately benefit the research patient.

In the history of clinical research there have been instances where the protections for human subjects were not honored, which has resulted in potential or actual harm to patients. The author conducted a literature review for instances of misconduct involving individual investigators and pharmaceutical companies. Documented research misconduct among contract research organizations was sparse.

With this information the author composed a questionnaire to assess the status of investigator perceptions of their relationship with sponsors and CROs. The author then considered the institution's internal research team, ranging from department leaders, research administrators, coordinators, regulatory personnel, and data team, and how their input would be valuable for a well-rounded assessment. The Capstone Project questionnaire was written in Google Docs for secure data collection and storage.

5.2.1. Questionnaire Distribution

The questionnaire titled *Clinical Research Stakeholders' Goals & Expectations* was distributed with Blind Carbon Copy (BCC) to eligible participants via institutional email with an embedded link to the Google Form. The email contained an IRB-approved email script (please see Appendix 2: Email Script) which explained the purpose of the questionnaire and eligible participants' rights as research subjects. One email was sent to eligible members of the Corporate Office of Research Operations (CORO), another email was sent to Adult Oncology Principal Investigators, and the last email was sent to Adult Oncology research staff.

5.3. Discussion of Questionnaire.

The author composed a questionnaire that contained 14 items for respondents to complete anonymously. There were two demographics questions, and nine multiple choice items graded on a five-point Likert scale using Strongly Agree, Agree, Neutral, Disagree, Strongly Disagree as responses. Several items added a "Not applicable" option, since the eligible participants espoused either clinical or non-clinical roles. For the questionnaire in its entirety please see Appendix 1: Questionnaire.

5.3.1. Demographics Items.

The author had two questions that dealt with obtaining general demographic information. The question, *How long have you worked in clinical research?*, with response choices ranging from "11+ years; 6-10 years; 2-5 years; 0-1 year" was asked in order to gauge the level of experience of the respondent and determine if the respondent had extensive or moderate experience at navigating clinical research regulations and conduct, or if they were a novice at conducting clinical research. If the

subject has many years of clinical research experience, they may have been exposed to instances of misconduct or lived through audit experiences that would have been an educational opportunity to them and the institution.

In another question, *What is your role at your institution? Select all that apply*, a respondent could check a box to indicate what role they have at their institution. They could choose from the following roles: Leadership; Clinical/ Principal Investigator; or Research Staff. This question was asked to determine the perspective of the respondent with regard to their role at the institution. Those in leadership have an operational view of research conduct, including onboarding clinical trials, supervising clinical and research personnel, and contributing to the overall vision of the department. Principal investigators are responsible for the clinical care and risks of their patients and are ultimately responsible for the conduct of the trial. Research staff have varied roles, including clinical research coordination and project management, data management, regulatory document submission and tracking, and quality assurance.

5.3.2. Multiple Choice Items.

There were nine multiple choice questions in the questionnaire with 5-point Likert Scale responses:

'My institution provides effective training on how to perform my role.' This item assessed the subject's perception on how the institution itself prepared them to perform their research role. The next item was, *I feel pressure to enroll more patients into clinical trials*, to reflect the potential of operational pressure to meet contractual accrual targets established at the initiation of a trial. "Not applicable" was included as a potential response. The institution is a member of the NRG cooperative groups within the

National Cancer Institute, which has an annual accrual target in order to maintain membership in the cooperative group.⁵²

In the third question, *I feel pressure to get investigational drugs/ devices/ doses approved for ordinary care*, respondents had Likert-scale responses to choose from, including “not applicable” as a choice for those that felt this statement did not apply to them. This question was asked to assess there was any pressure felt to have investigational products approved for standard of care uses, to assess whether this pressure could potentially overpower an investigator’s and institution’s equipoise in objectively studying an investigational agent.

The fourth question asked, *I have had concerns about clinicians pursuing off-label usage of drugs without IRB and FDA oversight*. Using a five-point “Adjectival Scale”⁵³, the item assessed whether first-hand knowledge exists of investigators potentially using investigational unapproved products on patients without proper regulatory and human research protections.

In the fifth multiple choice question, *I feel pressure to complete tasks unrelated to conducting or reviewing research* respondents could choose a 5-point Likert scale with the addition of “not applicable” for those that have no other roles competing for their time. The principal investigators at the author’s place of employment are also clinicians that see ordinary care patients. Those in leadership may have other administrative duties that require a considerable amount of effort apart from research conduct.

52. “Membership requirements,” NRG Oncology, accessed October 18, 2020, <https://www.nrgoncology.org/About-Us/Membership/Membership-Requirements>

53. Spencer E Harpe, “How to analyze Likert and other rating scale data,” *Currents in Pharmacy Teaching and Learning* no. 7 (2015): 838, <http://dx.doi.org/10.1016/j.cptl.2015.08.001>

The questions that followed were assessing the perception of the subjects' relationship with sponsors and CROs:

I receive effective protocol-specific training from external research partners (Sponsors or Contract Research Organizations). This item used a 5-point Adjectival scale and a "not applicable" option for those that do not receive training from sponsors or CROs. The item was written to assess if the subjects find value in the extensive training that sponsors and CROs require for initiating effort on studies.

The seventh question, *External research partners (Sponsors or Contract Research Organizations) are responsive to my site's needs*, with a five-point Adjectival scale ranging from "Always" to "Never" was used to see if subjects felt these entities were helpful and perceived a reciprocal relationship with regard to managing study challenges.

The eighth multiple-choice question, *Patient needs outweigh the need to adhere to the research protocol, even if it leads to a deviation*, allowed respondents to choose from a five-point Likert Scale with available responses, "Strongly Agree, Agree, Neutral, Disagree, Strongly Disagree", to tie the importance of patient safety in the clinician's mindset to the requirements of adhering to protocol procedures. The statement seeks to identify if the subject places more importance on the patient rather than the requirements of the protocol. One of the most common findings in an FDA audit is "failure to follow investigational plan (34%)"⁵⁴, however, some deviations involving the inability to conduct protocol procedures or follow dosing guidelines could be related to

54. Sonia K Morgan-Linnell, David J Stewart, and Razelle Kurzrock. "U.S. Food and Drug Administration Inspections of Clinical Investigators: Overview of Results from 1977-2009," *Clinical Cancer Research* 120, no. 13 (July 2014). <https://doi.org/10.1158/1078-0432.CCR-13-3206>

immediate patient safety or situations that investigators cannot foresee. For the final multiple-choice question, *My site has effective research partnerships that ultimately benefit the patient*, respondents were able to choose from a five-point Agree Likert scale. This item attempts to tie the relationships with internal and external entities to the ultimate goal of benefiting the patient.

5.3.3. Free-response Items.

At the latter part of the questionnaire, there are three free-response questions that allow the respondent to type in their response. These questions relate to multiple-choice items in the main section of the questionnaire:

Please feel free to comment on the effectiveness of your relationship with external research partners (Sponsors & Contract Research Organizations);

Please feel free to comment on any administrative challenges you encounter in your clinical research role; and

Please feel free to comment on how your involvement in research benefits the research patient.

With the free-response items, the authored hoped to solicit examples from the respondents that would provide insight to their selections in the multiple-choice items.

Chapter 6. Project Results and Discussion

6.1. Questionnaire Results.

Forty-four (44) potential subjects received recruitment emails with a total of 23 respondents, for a response rate of 52%. A challenge that became apparent upon distribution was that the Google Form link was blocked by the institutional firewall. The author received confirmation from their institutional Information Services that access to the Google Forms page link was not allowed per institutional policy. A small number of potential subjects reached out to the author and were guided to complete the questionnaire outside of the institutional firewall.

For data analysis, data were stratified by institutional role: research staff (n=10); or Clinical/ Principal Investigator (PI) and/or Leadership (n=13). The respondents that were purely Clinical/ Principal Investigators n=6; those that reported only Leadership roles n=4, and those that designated that they held both roles simultaneously were n=3. Please refer to Figure 2: N Clinical/ Principal Investigator & Leadership Respondents for a distribution of the investigator and leadership cohort:

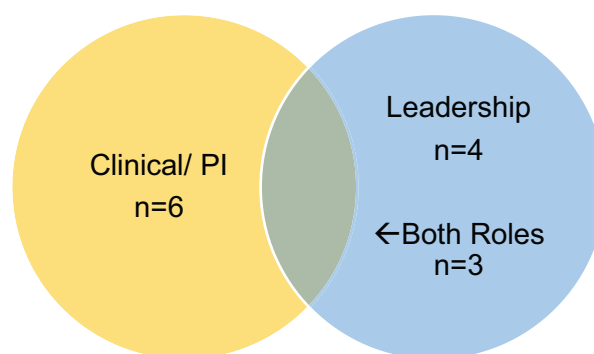


Figure 2. Number of Clinical/ PI & Leadership Respondents⁵⁵

55. Carolina Manchola-Orozco, November 1, 2020.

Respondents in the Clinical/ PI and leadership cohort all reported having greater than 6 years of experience (6-10 years n=2; 11+ years n=9) in clinical research, with the exception of one respondent in a leadership role who self-identified as having 2-5 years of research experience. 69% of this cohort reported greater than 11 years of experience in clinical research. Respondents who self-identified as research staff, half (50%) reported they had between 2-5 years of experience (n=5); and up to 6-10 years of experience (n=5) in clinical research.

For the purposes of statistical analysis, responses were given a numerical value. Items using the Likert Scale ranged from 5 for “Strongly Agree”, 4 for “Agree”, 3 for “Neutral”, 2 for “Disagree”, 1 for Strongly Disagree, and 0 for “Not Applicable”. Items using an Adjectival Scale were assigned the following values for their responses: 5 for “Always”, 4 for “Very Often”, 3 for “Sometimes”, 2 for “Rarely”, 1 for “Never”, and 0 for “Not Applicable”. The scoring values facilitated the calculation of the statistical mean and standard deviation for the individual responses, as suggested by Harpe⁵⁶ for analyzing Likert scales. Table 1. Assignment of Numerical Values for Scale Responses, demonstrates these values:

Table 1. Assignment of Numerical Values for Scale Responses⁵⁷

Likert Scale	Score	Adjectival Scale
Strongly Agree	5	Always
Agree	4	Very Often
Neutral	3	Sometimes
Disagree	2	Rarely
Strongly Disagree	1	Never
Not Applicable	0	Not Applicable

Response data was securely and anonymously collected via Google Forms. Once data

56. Spencer E Harpe, “How to analyze Likert and other rating scale data,” *Currents in Pharmacy Teaching and Learning* no. 7 (2015): 838, <http://dx.doi.org/10.1016/j.cptl.2015.08.001>

57. Carolina Manchola-Orozco, November 8, 2020.

collection was complete, all data was exported to a Microsoft Excel file. In the Excel file, data was sorted by Institutional Role, and responses were coded per the values shown in Table 1. The mean for each item was calculated (designated by μ) as well as the standard deviation (SD) of the responses (designated by σ).

6.1.1. Results Per Question.

The first question in the survey stated, *My institution provides effective training on how to perform my role*, and the responses were “Strongly Agree” to “Strongly Disagree” on a five-point Likert Scale. In the research staff cohort, the responses were overwhelmingly reported as “Agree” and “Strongly Agree”. There was only one response from a research staff member reported as “Neutral” The mean was $\mu=4.2$, and SD $\sigma=0.63$. The mean corresponds to a response of “Agree”.

In the Clinical/ PI and leadership cohort ($n=13$), responses provided insight into how the researchers and leaders felt about appropriate training provided by the institution. Question 3 prompted, *My institution provides effective training on how to perform my role*, with 5-point Likert scaled responses “Strongly Agree” to “Strongly Disagree”. Figure below shows the responses given, with responses distributed among the reported roles. Using the coded scores explained in Section 6.1.1 Table 1, $\mu=3.307$, and $\sigma=1.377$. The mean corresponds to a response of “Neutral”. Only 7/13 (53.8%) responded that they agreed or strongly agreed with this statement. Please see Figure 3. PI & Leader responses for effective Institutional training for a visual of how many respondents in each row selected a specific response:

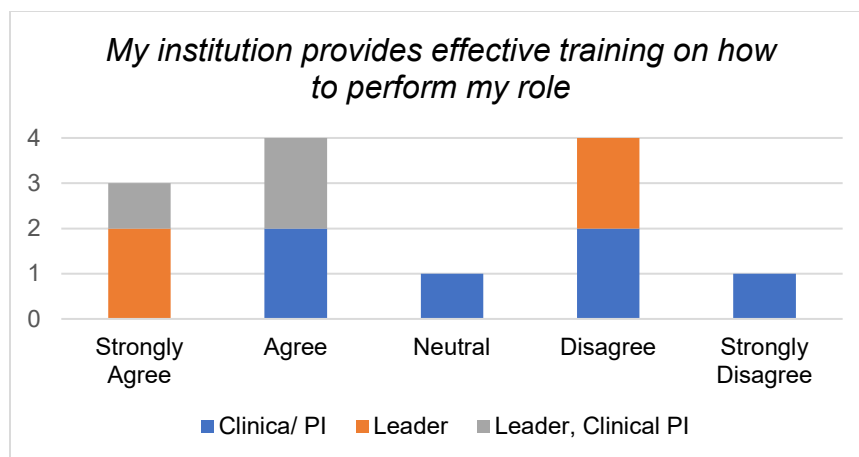


Figure 3. PI & Leader responses for Effective Institutional Training⁵⁸

The second statement in the survey said, *I feel pressure to enroll more patients into clinical trials*, with 5-point Likert scale responses to select from either, “Strongly Agree, Agree, Neutral, Disagree, Strongly Disagree, Not applicable”. The responses were coded with numerical values per Table 1. The mean $\mu=1.8$, which most closely represents “Disagree”, the mode (most reported response) was “Disagree”. The calculated SD $\sigma =1.398$ which describes the wider distribution of data present including the extreme lower end of the responses “Not Applicable”.

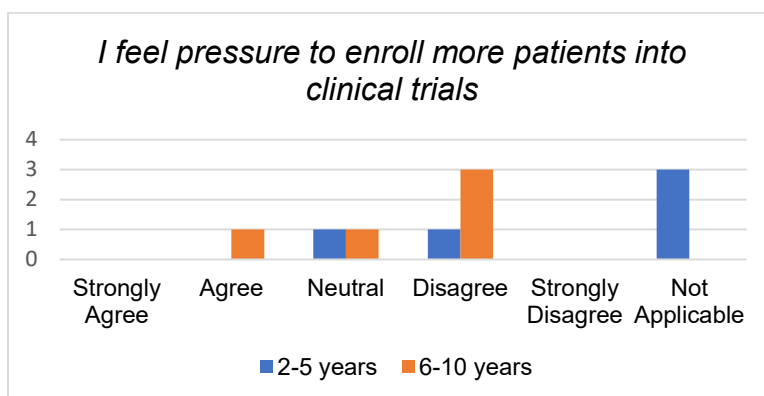


Figure 4. Responses for Pressure to Enroll Among Research Staff⁵⁹

Among the Clinical/ PI’s and leaders, the data suggests that this cohort mostly does not feel pressure to enroll subjects, with the exception of one individual that holds a

58. Carolina Manchola-Orozco, November 8, 2020.

59. Ibid.

Clinical/ PI role along with a leadership role; they chose “Strongly Agree”, as seen in Figure 5. below:

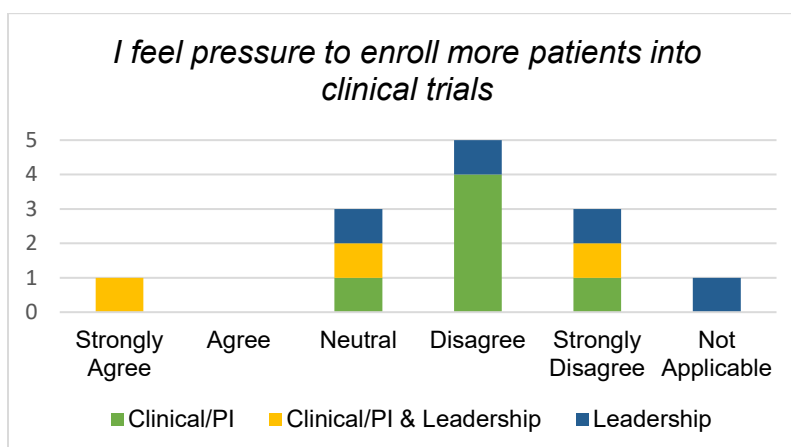


Figure 5. Responses for Pressure to Enroll among PI's & leaders⁶⁰

The mean $\mu=2.07$ (corresponding to “disagree”) and SD $\sigma=1.25$.

For the next statement in the questionnaire, *I feel pressure to get investigational drugs/ devices/ doses approved for ordinary care*, all of the respondents (n=23) in both cohorts combined answered either “neutral” 17.4%, “disagree” 39.1%, “strongly disagree” 30.4%, or “not applicable” 13%, $\mu=1.6$, $\sigma=0.94$.

The statement, *I have had concerns about clinicians pursuing off-label usage of drugs without IRB and FDA oversight*, most responses reported between “neutral”, “disagree” or “strongly disagree”. There were two respondents in the PI & Leadership cohort that responded “Agree”, one that was purely a PI, and the other had combined PI and Leadership roles. Among all subjects, the mean $\mu=1.82$, SD $\sigma=0.88$.

The next item on the questionnaire was *I feel pressure to complete tasks unrelated to conducting or reviewing research*. The responses were on an Adjectival scale; respondents had the option of choosing “Always, Very Often, Sometimes,

60. Carolina Manchola-Orozco, November 8, 2020.

Rarely, Never”. The majority of the respondents chose “sometimes”, “rarely”, or “never”, $\mu=2.333$, $SD \sigma=1.302$. One respondent in a leadership role selected “very often”, and the other in a combined PI and leadership role chose “always”, as seen in Figure 6.

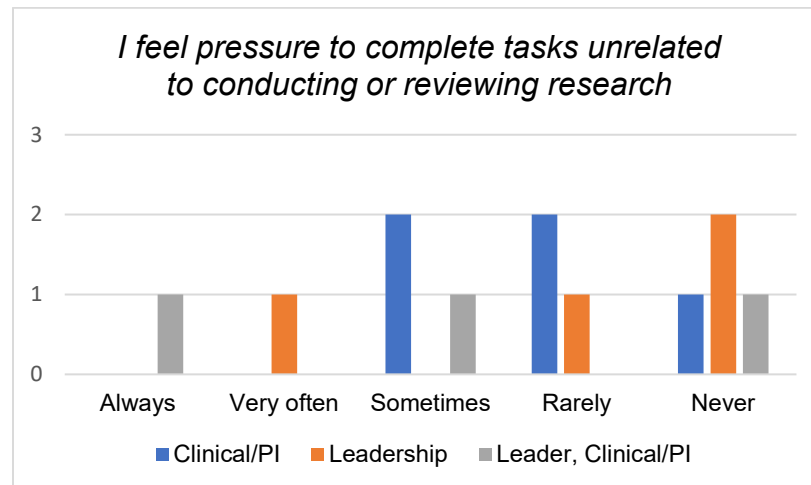


Figure 6. PI & Leader Pressure to Complete Unrelated Tasks⁶¹

In the research staff cohort, 70% chose “strongly disagree”, while 20% selected “sometimes”, and 10% “not applicable”, mean $\mu=1.3$ which corresponds to “strongly disagree”, $SD \sigma= 0.948$. These results are unsurprising since the research staff are hired specifically to complete research-related tasks.

The following item, *I receive effective protocol-specific training from external research partners (Sponsors or Contract Research Organizations)*, principal investigators and leaders had a wide distribution of responses, as demonstrated by the calculated mean $\mu=3.38$, $SD \sigma=1.6602$. Figure 7. PI & leader reports of effective external training shows the responses:

61. Carolina Manchola-Orozco, November 8, 2020.

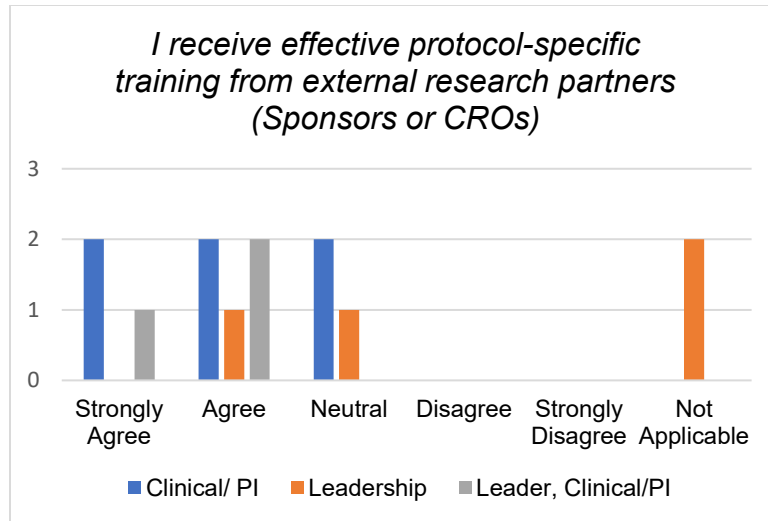


Figure 7. PI & Leader Reports of Effective External Training⁶²

The research staff cohort had a calculated mean $\mu=4.2$, which corresponds to “Agree”, with a SD $\sigma=0.9189$. As reported below in Figure 8, most responses were “strongly agree” or “agree”.

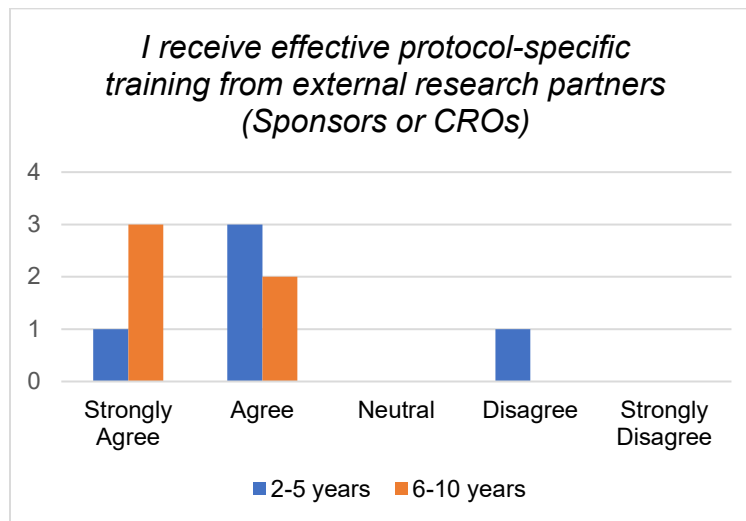


Figure 8. Research Staff Report of Effective External Training⁶³

The next statement was *External research partners (Sponsors or Contract Research Organizations) are responsive to my site's needs*. The answers were on a

62. Carolina Manchola-Orozco, November 8, 2020.

63. Ibid.

five-point Adjectival scale, with responses ranging from “Always” to “Never”. Using the entire set of responses (n=23), the mean $\mu=4$, SD $\sigma=0.738$. The mean corresponded to the response “very often”. There were no responses for “strongly disagree” or “not applicable” as shown in Figure 9:

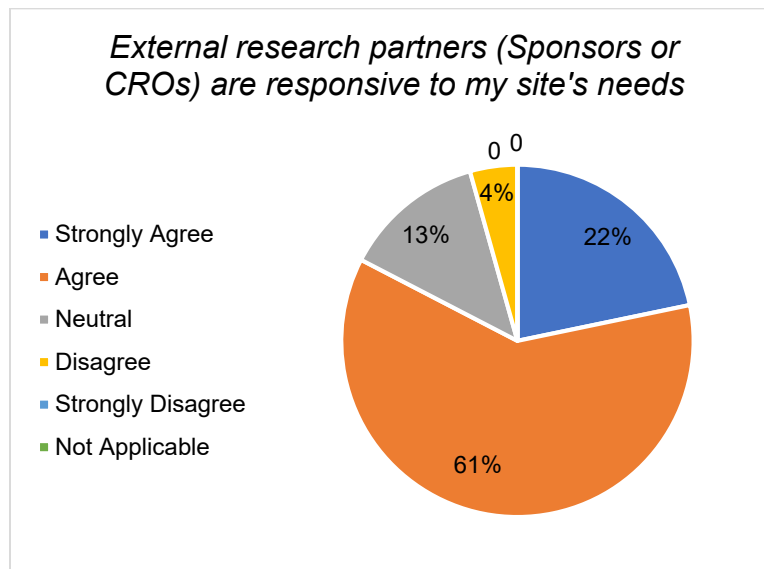


Figure 9. Responses for Partners are Responsive to Site Needs⁶⁴

The penultimate item, *Patient needs outweigh the need to adhere to the research protocol, even if it leads to a deviation*, had respondents select from a 5-point Likert scale using “Strongly Agree” to “Strongly Disagree”. Among the PI & Leadership cohort, the mean $\mu=3.769$, $\sigma= 1.235$. Figure 9. PI & Leader response: patient needs vs protocol deviation shows the distribution of responses:

64. Carolina Manchola-Orozco, November 8, 2020.

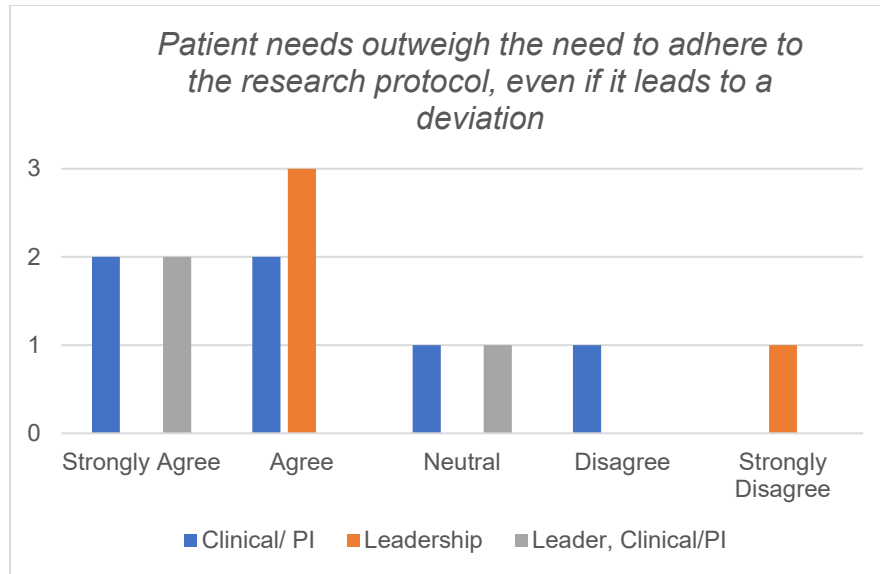


Figure 10. PI & Leader Response: Patient Needs vs Protocol Deviation⁶⁵

Among the research staff, the mean $\mu=4$, and SD $\sigma=1.1547$. The mean of 4 corresponds to a mean for the response “agree”. In Figure 11. Research staff patient needs vs protocol deviation, shows the wider distribution of responses for the research staff cohort, compared to responses to other items in the survey:

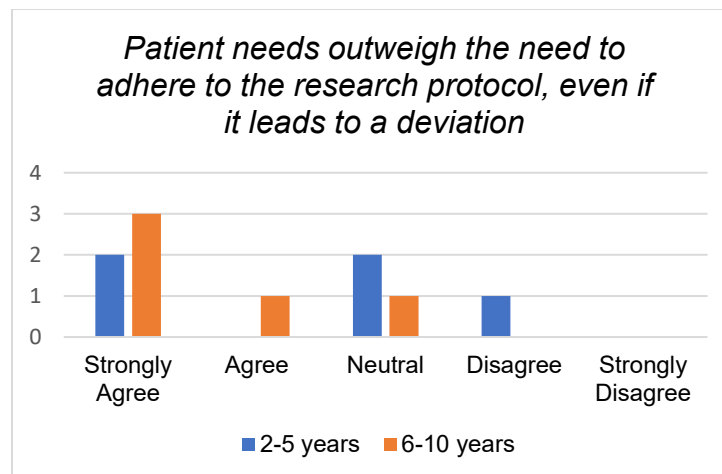


Figure 11. Research Staff: Patient Needs vs Protocol Deviation⁶⁶

65. Carolina Manchola-Orozco, November 8, 2020.

66. Carolina Manchola-Orozco, November 11, 2020.

This particular item on the questionnaire had a higher standard deviation in both cohorts, which demonstrates that the agreement with the statement is varied throughout the practice in all roles.

The last item, *My site has effective research partnerships that ultimately benefit the patient*, had respondents select from “Strongly Agree” to “Strongly Disagree”. Figure 12. Responses for effective partnership that benefit patients shows how 61% of the entire cohort chose “Agree”, 30% “Strongly Agree”, and 9% responded “Neutral”:

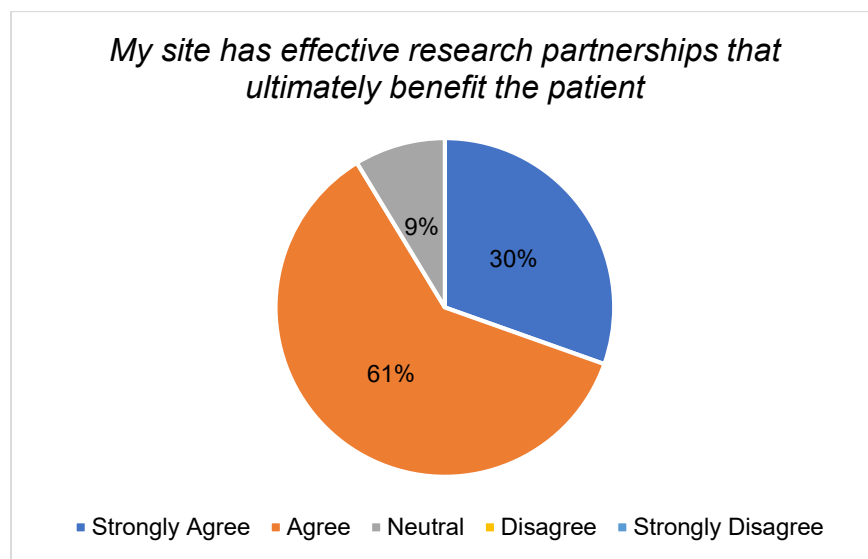


Figure 12. Responses for Effective Partnerships that Benefit Patients⁶⁷

The calculated mean among all participants was $\mu=4.217$, and the smallest SD of the entire survey $\sigma=0.599$. This particular result was pleasing to note that investigators, leaders, and research staff at large feel that the external partnerships with sponsors and contract research organizations benefit the patient.

⁶⁷. Carolina Manchola-Orozco, November 8, 2020.

Chapter 7. Recommendations and Discussion

7.1. Introduction.

The questionnaire results have important observations with regard to PI, leadership, and research staff perceptions on their relationships with external clinical research stakeholders, and perceptions on the effectiveness of internal research infrastructure. Institutional policies and continuing education for staff are meant to protect against research misconduct. Sponsors and CROs each have their goals and expectations for their respective roles in the research enterprise, and all stakeholders have a responsibility to balance their goals with their collaborators' goals in order to efficiently bring new therapeutics to market. To further assist the sites with initiating their relationship with sponsors and CROs, a Site Qualification Tool is proposed by the author to increase site engagement prior to contractually initiating a research collaboration.

7.2. Recommendations.

7.2.1. Operational Observations and Recommendations.

7.2.1.1. Recommendation 1: The Institution should re-examine how PI and Research Leaders are Trained and Retool the Training so that PIs and Research Leaders can Improve their Effectiveness.

The questionnaire collected observations from institutional research leadership, investigators, and staff that research leaders can consider in making operational improvements. The statement, *My institution provides effective training on how to perform my role*, had 38% of the PI's and leaders either disagree or strongly disagree with that assertion. It would be helpful for the institution to re-examine how they train

their principal investigators (PIs) and research leaders and retool the training the institution can provide for this population to perform their role effectively. This questionnaire did not delve into the types of training or topics that would meet the needs of the investigators and leaders, so further inquiry would be helpful to address the training gap. If the institution is not able to provide their own educational programming for PIs and leaders, there are various professional organizations that are suited for training and certifying research investigators and administrators. The Association of Clinical Research Professionals (ACRP)⁶⁸ has online coursework that serves to educate clinical researchers that are either entry, intermediate, or senior level, within a wide variety of topics including Good Clinical Practice, Quality Assurance, and leadership strategies. The ACRP offers certifications for research coordinators and research monitors, and a certification for Principal Investigators called Certified Principal Investigator (CPI). The Society of Research Administrators International (SRAI)⁶⁹ is a professional organization that offers extensive training for research administrators and research leaders. One such training offered is a “Research Senior Executive Institute.”⁷⁰ The data from research staff suggests that they receive appropriate training. This is a testament to the institution’s strong focus on educational modules for research coordinators and support staff.

68. “ACRP Course Catalog,” Association of Clinical Research Professionals, 2020, <https://acrpnet.org/training/>

69. “Trainings and Conferences,” Society of Research Administrators International, 2020, <https://www.srainternational.org/meetings/trainings-conferences>

70. Ibid.

7.2.2. Concerns about clinicians pursuing off-label usage of drugs without IRB and FDA oversight.

7.2.2.1. Recommendation 2: The Institution Should Have a Research Integrity Officer (RIO) that is Dedicated Solely to Investigating Allegations of Research Misconduct.

With regard to the question that asked if respondents had *concerns about clinicians pursuing off-label usage of drugs without IRB and FDA oversight*, there were respondents from leadership that expressed concern. This question did not ask when these concerns occurred or if the concerns were still present, only if they had occurred. There is opportunity for further review of these instances which herald the potential for scientific misconduct. A recommendation for the institution would be to have a Research Integrity Officer (RIO) that is dedicated solely to investigating allegations of research misconduct. The ORI Handbook for Institutional Research Integrity Officers from the Office of Research Integrity of the US DHHS, is “a reference work for institutional officials who have responsibilities regarding the handling of allegations of scientific misconduct involving biomedical or research training.”⁷¹

The “ORI also encourages institutions to adopt principles consistent with the Whistleblower Bill of Rights recommended by the Commission on Research Integrity and to foster institutional commitment to those principles.”⁷² Increasing training initiatives on whistleblower protections would be recommended for institutional adherence to the ORI. According to Bonito, Titus, and Wright, findings from a “study

71. “ORI Handbook for Institutional Research Integrity Officers,” Office of Research Integrity, n.d., https://ori.hhs.gov/sites/default/files/rio_handbook.pdf

72. “Handling Misconduct – Whistleblowers”, Office of Research Integrity, last modified November 20, 1995, <https://ori.hhs.gov/content/guidelines-whistleblowers>

found that 9% of PHS funded researchers reported observing possible research misconduct in the prior 3 years,⁷³ which is in alignment with the institution's rate of concerned investigators in this sample.

7.2.3. Lack of Institutional support for clinical research

7.2.3.1. Recommendation 3: The Institution Should Listen to its Internal Research Stakeholders and Become Well-poised to Continue Developing its Clinical Research Venture.

Institutional goals for research include having successful collaborations with sponsors which can lead to further collaboration and referrals to other sponsors. New research partnerships increase research-related funding and contracts with industrial pharmaceutical companies. Ultimately institutional reputation can elevate among the medical community, making the institution more competitive in recruiting top research talent and leadership. The institution has the ability to achieve prominence with its academically prolific oncology investigators. Commentary among the respondents of the questionnaire include the following from several that hold both Leadership and Principal Investigator roles: "I don't think my institution values clinical research, in general, as much as other university based institutions. I sometimes feel the default answer is 'no', rather than 'let me see what this is about.'"⁷⁴ Another subject with dual leader and PI roles commented, "For most clinicians, there is no protected time to conduct research, which takes extra time. RVU [Relative Value Units] incentivized

73. Arthur Bonito, Sandra Titus, and David Wright, "Assessing the Preparedness of Research Integrity Officers (RIOs) to Appropriately Handle Possible Research Misconduct Cases" *Science and Engineering Ethics*, 18 (2012): 605-619. <https://doi.org/10.1007/s11948-011-9274-2>

74. Questionnaire respondent, October 31, 2020

physicians have a financial disincentive to enroll and take extra care of patients wrt [sic] documentation, etc.”⁷⁵ In this community hospital setting, discussion should be considered to cease penalizing physician-scientists that wish to devote time to research activities and away from filling their clinic patient quota. A third leader/ PI exclaimed, “We are seeking a director position that will provide leadership to the team.”⁷⁶ This is hopefully a harbinger of positive developments to come. One research staff member commented, “There is always room for growth and we can always do more to help our community by listening to the needs of our patients, physicians, and team members, come up with a process or a plan to expand our research vision and institution.”⁷⁷ If the institution wishes, and is prepared to listen to its internal research stakeholders, it is well-poised to continue developing its clinical research venture.

7.2.4. Further enhancements to the existing compliance and quality assurance efforts.

7.2.4.1. Recommendation 4: The Institution Should Have a Quality Assurance Team Specific to the Adult Oncology Department.

The institution has a number of mechanisms that have been adopted to ensure regulatory compliance, and meet contractual obligations with regard to recruitment, subject safety reporting, and data quality. The institution has their own Institutional Review Board (IRB) that reviews and approves studies in adult and pediatric populations. Research staff, PIs and sub-investigators meet biweekly at minimum to discuss potential subjects, subjects undergoing active treatment, protocol

75. Questionnaire respondent, October 23, 2020.

76. Questionnaire respondent, November 2, 2020.

77. Questionnaire respondent, October 29, 2020.

deviations, serious adverse event reporting, and preparation for monitoring visits. This has created an environment where staff and clinical investigators are engaged and converse on important topics for their respective cancer types. There is also an institutional Quality Assurance initiative that employs internal auditors that review research documentation in all of the clinical research departments within the hospital. One suggestion the author offers is to have a Quality Assurance team specific to the adult oncology department, as there are two internal auditors for the entire institution. This initiative would add another layer of quality control for research subject data and regulatory documentation in addition to standard external monitoring visits.

7.2.5. Sponsor & CRO Goals and Discussion.

Sponsors control and design clinical research studies, and take “responsibility for the initiation, management, and/or financing of a clinical trial.”⁷⁸ A sponsor can be an individual, or a pharmaceutical manufacturer of an investigational product. A sponsor can partner with pharmaceutical companies that allow them to use their investigational products, much like cooperative groups and scientists within the National Cancer Institute. “Before testing the product in the clinical phase, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at potential dosages, for the duration, and in the trial population to be studied.”⁷⁹ In addition to reporting prior safety data,

The sponsor is responsible for the ongoing safety evaluation of the investigational product. The sponsor should promptly notify all concerned

78. Deepak Chilkoti. 2019. “Chapter 25: Stakeholders, Resources, and Documents in Clinical Research.” In *Clinical Pharmacy Education, Practice and Research*, 365-377. Elsevier Inc. <https://doi.org/10.1016/B978-0-12-814276-9.00025-8>

79. Ibid.

investigators/institutions and the regulatory authority of findings that could affect the safety of subjects or alter the IRB/IEC's [Independent Ethics Committee] approval opinion to continue the trial.⁸⁰

Sponsor goals are to develop compounds that may be shown to be effective in multiple indications in order to maximize return on their investment to develop an investigational product. As reported in section 2.2.5.3. Sponsor Misconduct, these goals have historically become unbalanced with sponsor greed and potentially harmed vulnerable populations by violations against the False Claims Act, or failure to report safety data that may lead a clinical trial to be halted or an approved product to be pulled from the market.

CROs are contracted to sponsors to assist sponsors in managing clinical trial operations. As part of a CRO, Clinical Research Associates (CRA) have the following roles:

managing approvals that oversee the research and marketing of new and existing drugs; identifying and assessing the suitability of facilities to be used as the clinical trial site; monitoring the trial throughout its duration; verifying that data entered... are consistent with patient clinical notes, source data/document verification; writing visit reports...; ensuring all unused trial supplies are accounted for...; archiving study documentation and correspondence”⁸¹

As the research enterprise comes to terms with misconduct and Good Clinical Practice guidance, operational procedures seek to find equilibrium between hyper-regulation and lack of proper oversight. One item in the questionnaire asked subjects to comment on any administrative challenges they encounter in their clinical research role. One questionnaire respondent in a PI role shared, “The AE [adverse event] reporting and review portals are not well designed They change to [sic] frequently for sponsors. Very

80. Deepak Chilkoti. 2019. “Chapter 25: Stakeholders, Resources, and Documents in Clinical Research.” In *Clinical Pharmacy Education, Practice and Research*, 365-377. Elsevier Inc. <https://doi.org/10.1016/B978-0-12-814276-9.00025-8>

81. Ibid.

amateurish in their ease of use.”⁸² When asked to comment on the effectiveness of their relationship with sponsors and CROs, a respondent with dual roles as a PI and leader said, “Many are very responsive, some that are smaller organizations are less responsive.”⁸³ A research staff member shared, “good and timely communication helps both parties in order to give the best care to the patients.”⁸⁴ As sponsors and CROs navigate changing requirements with monitoring and safety reporting, when all stakeholders approach the partnership in the spirit of good communication, the patients ultimately benefit from transparent collaboration dedicated to process improvement.

7.2.6. Patient Focus.

The ultimate goal of researchers is to provide tangible benefit to the patients that volunteer their lives to participate in a clinical trial. As part of the informed consent process, patients are educated about what the potential risks of participation are, what their options are outside of research participation, and how there are many different teams that are overseeing the research conduct to ensure that their safety and rights are protected. A respondent holding a leadership and PI role exclaimed,

I have had many patients get beneficial and life saving treatments way before FDA approval. In addition, the extra supervision provided by research staff, pharmacy and IRB makes this a much safer treatment than standard treatment, even when the drugs are very new.⁸⁵

Seeing these physicians engaged in the research process while holding the patient experience in the highest regard fosters a positive culture among other investigators and research staff. A research staff member shared,

82. Questionnaire respondent, November 1, 2020.

83. Questionnaire respondent, November 2, 2020.

84. Questionnaire respondent, October 26, 2020.

85. Questionnaire respondent, October 31, 2020.

Caring about our community our patients our department and team members has been the number one key to my involvement and be part of studies that have been approved by the FDA which is now a standard of care option for our patients whom are currently living a better quality of life and at times longer than expected. I would say that is the most rewarding experience and benefit for our community and patients.⁸⁶

For many years cancer patients and their caregivers have formed organizations that offer support to patients and their families. Many of these offer emotional support, financial resources, and assistance in finding clinical trials that patients can hopefully participate in. Some organizations are devoted to a specific cancer type, or offer help for a certain population. An exciting development in the clinical research world is seeing patients themselves advocating for changes to how research is conducted. According to Wingfield, who was himself a research participant-turned IRB professional,

We gave input on whether we thought the research was needed in our local community and if the design of the research was fair to the participants... We were not just a figurehead group to satisfy network funding requirements. Our opinions were actively sought and respected by the researchers in the clinics.⁸⁷

The clinical trials industry is now incorporating patient advocacy and feedback in clinical trial design on a large scale. The Patient-Centered Outcomes Research Institute (PCORI) is a cooperative research group that is conducting studies in the United States and Canada, and working to increase minority participation in clinical trials. Their mission states:

PCORI helps people make informed healthcare decisions, and improves healthcare delivery and outcomes, by producing and promoting high-integrity, evidence-based information that comes from research guided by patients, caregivers, and the broader healthcare community.⁸⁸

This is a large organization that has “funded more than \$2 billion in research and related

86. Questionnaire respondent, October 26, 2020.

87. Harry Wingfield. Human Subjects Research: An Insider's View (Independently published, 2020), 31.

88. “About us.” PCORI, accessed November 17, 2020, <https://www.pcori.org/about-us>

projects... [they] also provide funding to help more patients and other stakeholders become involved in the research process.”⁸⁹ Research professionals are embracing patient suggestions and including patients in the design of clinical trials. There is greater engagement of the patient population which has altered the very structure of how clinical research is conducted. The hope is that this will encourage clinical trial participation by inviting patients into a larger clinical trial community.

7.2.7. Unilateral study initiation process does not verify sponsor qualifications.

7.2.7.1. Propose a Sponsor Qualification Tool to Examine the Sponsor’s and CROs Ability to Support the Site Throughout the Conduct of the Clinical Trial.

When a sponsor or a site expresses interest in clinical trial collaboration, typically the parties sign a Non-disclosure agreement, to ensure confidentiality of the proprietary information that will be shared. Once this is signed, the sponsor can then share details of the study, and the site can decide if conducting the study is feasible at their center. Traditionally the sponsor conducts a Site Qualification Visit, where a sponsor or Contract Research Organization (CRO) representative conducts an in-person visit at the site, looking at the facilities, personnel, standard operating procedures, and determining if the site has the experience to meet the sponsor’s requirements throughout the trial. The author has facilitated many of these Site Qualification Visits at multiple institutions, guiding sponsor and CRO representatives through the different divisions of an oncology research practice.

89. “About us.” PCORI, accessed November 17, 2020, <https://www.pcori.org/about-us>

As described, the pre-contract trial qualification process is unilateral- there has been no sponsor qualification conducted to determine if the sponsor's infrastructure would adequately support the site throughout the conduct of the trial. The author proposes a Sponsor Qualification Tool⁹⁰ (please see Appendix 3. Sponsor Qualification Tool) to allow sites to assess whether the sponsor has the expertise to run a clinical trial before they execute an agreement to accept a research protocol. The tool is separated into categories including Sponsor demographics, Contractual & Financial Terms, CRO oversight, and Trial execution. Trial execution includes the sub-categories Recruitment, Equipment, and Protocol assessments.

The initial items on the tool will ask for general information, such as the study name, study number, and study chair. The investigational product and IND number, and indication under study are also requested. An important question to ask is who is supplying the investigational product? Is it supplied by the sponsor, or sourced via commercial supply? The form also asks for the name of the sponsor, a name of the sponsor representative, and contact information. Sponsor demographics will inquire how many studies they have conducted with the study cancer, how many Investigational New Drug (IND) approvals do they hold for the indicated cancer, and how many New Drug Applications (NDA) have been filed with the FDA in the last 5 years. How many studies have they attempted for this particular investigational product? Have they been inspected by the FDA and what was the outcome? Was the FDA inspection 'for cause' or 'routine'?

The Contractual & Financial Terms section covers general contractual terms. The

90. Carolina Manchola-Orozco, November 2020.

questions on the assessment include:

1. Who are the key personnel required on the study?
2. What are your deliverables?
3. How often do you pay sites?
4. What is your indemnification policy?
5. What is your data ownership policy?
6. What is your intellectual property policy (including patent and copyright material)?
7. What is the average length of time to finalize contract negotiations?
8. Will a final budget be available prior to contract negotiations?
9. Which procedures is the sponsor considering Ordinary Care/ Standard of Care that Medicare may not cover?

The purpose of these questions is to pre-empt any terms that may not be acceptable to the site, allowing the site to have an opportunity to decide if any of those terms warrant negotiation prior to contract execution.

The CRO Oversight questions are intended to evaluate the potential CRO that is contracted to assist the site with study conduct:

1. How many studies has the CRO conducted on the study cancer?
2. What is the rate of Clinical Research Associate (CRA) turnover in the last 3 years?
 - 2a. On average how many monitors have been assigned to a single study in the last 3 years?
3. Will monitors conduct remote Site Initiation Visits (SIV) and Interim monitoring visits (IMV)?
4. Has the CRO successfully conducted virtual SIVs and IMVs?

Note: The institution will not allow source documentation to be uploaded to any external document repository. The institution will provide cloud-based document storage that study monitors can securely access.
5. What is the Electronic Data Capture (EDC) program?
6. Will the CRO hold periodic meetings for PIs or study coordinators?

The following section of the Sponsor Qualification Tool is for Trial execution. The recruitment questions include: What is your expected annual subject accrual rate? What recruitment materials are provided? Will document translation (for Informed Consents

and protocol-required assessments) be paid by the sponsor? If a translated Informed Consent form is not available, can the site use a Short Form Consent Form?

The Equipment section will include: What equipment will the sponsor provide? What facilities and equipment do you expect from the recruiting site? The Protocol Assessments section will include the following: Are there central assessments? Please indicate all that apply: Laboratory, Imaging, Disease Response Assessment, and other.

The questions above serve as a starting point for the sponsor and CRO to be more forthcoming regarding their capabilities prior to initiating a clinical trial. The hope is to empower research sites to ask sponsors and CROs questions and determine if their site's needs can be met during study initiation and study recruitment, finding effective resolution of issues with the investigational product and adverse events, and periodic monitoring of the study data.

Chapter 8. Conclusion

The author examined the connection between stakeholders involved in the clinical research enterprise, and their respective roles and goals. These stakeholders include the sponsor, contract research organizations, principal investigators, and the research institution. At the center of the complementary entities are the patients that put their trust in the clinical research system to give themselves hope, and contribute to and advocate for clinical research. Adult oncology Principal Investigators, Leaders, and Research Staff at the author's community hospital research practice graciously contributed to the conduct of this Capstone Project. There were areas identified for further investment within the institution's clinical research infrastructure. The author has offered operational enhancements for the institution and created a Sponsor Qualification Tool that will empower clinical research sites to determine if a sponsor and CRO are suitable for a productive and symbiotic partnership.

The need for biomedical innovation has accelerated, and the need for research sites that can contribute quality data and sponsors that can design meaningful science is ever-growing. Research institutions with unestablished or inefficient research infrastructure can benefit from knowledge of stakeholder relationships and the risks of misconduct from sponsors, CROs, PIs, and the research institution itself. Risk mitigation and stakeholder engagement empower human subjects.

In the history of clinical research there have been instances where actions among stakeholders have caused harm to patients and diminished trust in the scientific community. As evidenced in the long-term changes to federal regulations and Good Clinical Practice guidance, the country's regulatory authorities and the clinical research

industry have taken significant steps to reduce the risk of research misconduct. This serves as a beacon for all stakeholders to engage in the evolution of human subject protections.

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Appendix 1. Questionnaire

INTRODUCTION

I am Carolina, research coordinator in Adult Radiation Oncology and Neuro Oncology.

This questionnaire is on goals and expectations that clinical trial research stakeholders at Research sites may experience. By completing this questionnaire, you are consenting to participate in this project. Your participation is voluntary and you can stop at any time and skip any questions. This questionnaire should not take more than 10 minutes of your time.

For the purposes of this questionnaire, a Research site is an institution where Human Subjects research is conducted.¹ A sponsor is the organization or investigator “who initiated the study and who has authority and control over the study.”² A contract research organization is “a company hired by another company or research center to take over certain parts of running a clinical trial. The company may design, manage, and monitor the trial, and analyze the results.”³

The feedback you provide will be used in support of the Capstone Project I am completing as a requirement for the Master of Science in Research Administration at Johns Hopkins University. Your responses are anonymous and will be analyzed for this Capstone Project.

If you have any questions or concerns regarding this Questionnaire, please contact me at cmancho1@jh.edu. If you have concerns or complaints about the research, or questions about your rights as a research subject, please contact the Orlando Health IRB at (321) 841-5895.

I greatly appreciate your time.

1. How long have you worked in clinical research?

- ☐ 11+ years
- ☐ 6-10 years
- ☐ 2-5 years
- ☐ 0-1 year

1. 45 CFR 46.102

2. Glossary of Common Site Terms, s.v. “Sponsor,” accessed September 18, 2020, <https://clinicaltrials.gov/ct2/about-studies/glossary>.

3. NCI Dictionaries, s.v. “Contract Research Organization,” accessed September 18, 2020, <https://www.cancer.gov/publications/dictionaries/cancer-terms/def/contract-research-organization>

2. What is your role at your institution? Select all that apply

- ☐ Leadership
- ☐ Clinical/ Principal Investigator
- ☐ Research Staff

3. My institution provides effective training on how to perform my role

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree

4. I feel pressure to enroll more patients into clinical trials

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree
- ☐ Not Applicable

5. I feel pressure to get investigational drugs/ devices/ doses approved for ordinary care

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree
- ☐ Not Applicable

6. I have had concerns about clinicians pursuing off-label usage of drugs without IRB and FDA oversight

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree

7. I feel pressure to complete tasks unrelated to conducting or reviewing research

- ☐ Always
- ☐ Very often
- ☐ Sometimes
- ☐ Rarely
- ☐ Never
- ☐ Not Applicable

8. I receive effective protocol-specific training from external research partners (Sponsors or Contract Research Organizations)

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree
- ☐ Not Applicable

9. External research partners (Sponsors or Contract Research Organizations) are responsive to my site's needs

- ☐ Always
- ☐ Very often
- ☐ Sometimes
- ☐ Rarely
- ☐ Never

10. Patient needs outweigh the need to adhere to the research protocol, even if it leads to a deviation

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree
- ☐ Not Applicable

11. My site has effective research partnerships that ultimately benefit the patient

- ☐ Strongly Agree
- ☐ Agree
- ☐ Neutral
- ☐ Disagree
- ☐ Strongly Disagree

Please feel free to comment on the effectiveness of your relationship with external research partners (Sponsors & Contract Research Organizations):

Please feel free to comment on any administrative challenges you encounter in your clinical research role:

Please feel free to comment on how your involvement in research benefits the research patient:

Thank you for your time!

Appendix 2. Email Script

Hello,

You are receiving this because you are an investigator, leader, or research staff within Adult Oncology Research or the Corporate Office of Research Operations.

I am Carolina Manchola-Orozco CCRP, Clinical Research Coordinator in Adult Radiation & Neuro Oncology. I would greatly appreciate if you could complete and submit this questionnaire for my Capstone project as a requirement of a MS in Research Administration at Johns Hopkins University.

Project Title:

Clinical Research Stakeholders' Goals and Expectations

Principal Investigators:

Johns Hopkins University – Marianne Woods PhD, JD

Orlando Health – Naren Ramakrishna MD, PhD

Attached is a link to a questionnaire that assesses your goals, expectations, and challenges as you conduct clinical research activities here and with Sponsors and Contract Research Organizations (CROs). This study will explore factors that may protect against research misconduct in your interactions with institutional staff, Sponsors, and CROs.

There are no direct benefits, and you will not be compensated for participating. Your participation is anonymous and voluntary, and you can skip any questions. Data will be collected and securely and confidentially stored via a Google Docs form. Neither your email address nor your IP address will be recorded. The Principal Investigator at Johns Hopkins and I will have access to your data for the purpose of data analysis and reporting. Completing this should take less than 10 minutes of your time.

If you have any questions or concerns regarding this Questionnaire, please contact me at cmancho1@jh.edu. If you have concerns or complaints about the research, or questions about your rights as a research subject, please contact the Orlando Health IRB at (321) 841-5895.

Thank you!

Carolina Manchola-Orozco CCRP

Appendix 3. Sponsor Qualification Tool

Sponsor Qualification Tool

Please complete all of the questions below.

If you have any questions please reach out to your Regulatory Coordinator:

Name: _____ Office #: _____ Email: _____

Study Name: _____

Study Number: _____ Study Chair: _____

Investigational Product: _____ IND #: _____

Indication under study: _____ Product Supplied by: ☐ Sponsor ☐ Commercial

Sponsor Name: _____

Sponsor Representative: _____

Sponsor Contact Information (telephone/ email): _____

Sponsor Demographics:

1. How many studies have you conducted with the study cancer? _____
2. How many Investigational New Drug (IND) approvals do you hold for the indicated cancer? _____
3. How many New Drug Applications have you filed with the FDA in the last 5 years? _____
4. How many studies have you attempted for this particular investigational product? _____
5. Have you been inspected by the FDA? *Circle one:* Yes / No
 - 5a. If yes, what was the outcome? _____
 - 5b. Why was the FDA inspection conducted? *Circle one:* For Cause / Routine

Contractual & Financial Terms:

1. Who are the key personnel required on the study? _____
2. What are your deliverables? _____
3. How often do you pay sites? _____
4. What is your indemnification policy? _____
5. What is your data ownership policy? _____
6. What is your intellectual property and licensing policy (including patent and copyright material)? _____

7. What is the average length of time to finalize contract negotiations? _____ months
8. Will a final budget be available prior to contract negotiations? Yes / No
9. Which procedures are the sponsor considering Ordinary Care/ Standard of Care that Medicare may not cover? _____

CRO Oversight:

1. How many studies has the CRO conducted on the study cancer? _____
2. On average how many monitors have been assigned to a single study in the last 3 years? _____
3. Will monitors conduct remote Site Initiation Visits (SIV) and Interim monitoring Visits (IMV)? *Circle one:* Yes / No
4. Has the CRO successfully conducted virtual SIVs and IMVs?
Note: The institution will not allow source documentation to be uploaded to any external document repository. The institution will provide cloud-based document storage that study monitors can securely access.
5. What is the Electronic Data Capture (EDC) program? _____
6. Will the CRO hold periodic meetings for PIs or study coordinators? *Circle one:* Yes / No

Trial Execution:

1. What is your expected annual subject accrual rate? _____ per year
2. What recruitment materials are provided? _____
3. Will document translation (for Informed Consents and protocol-required assessments) be paid by the sponsor? *Circle one:* Yes / No
4. If a Consent Form is not available, can the site use a Short Form?
Circle one: Yes / No

Equipment:

1. What equipment will the sponsor provide? _____
2. What facilities and equipment are expected from the recruiting site? _____

Protocol Assessments:

1. Are there Central assessments? *Circle one:* Yes / No
- If Yes, please indicate all that apply:
- ☐ Laboratory ☐ Disease Response Assessment
- ☐ Imaging ☐ Other: _____

Thank you for completing the Sponsor Qualification Tool.

Name of person completing form: _____ Contact information: _____

Signature: _____ Date: _____ dd/mmm/yyyy

For Internal Use:

Internal Reviewer: _____

Date: _____ *dd/mmm/yyyy*

Appendix 4. Homewood Institutional Review Board Acknowledgement



Homewood Institutional Review Board

3400 N. Charles Street
Wyman Park Building, Suite N468
Baltimore MD 21218-2685
410-516-6580
<http://homewoodirb.jhu.edu/>

Michael McCloskey, PhD
IRB Chair

Date: October 22, 2020

PI Name: Marianne Woods

Study #: HIRB00011867

Study Name: Clinical Research Stakeholders' Goals and Expectations

Date of Review: 10/21/2020

Date of Acknowledgement: 10/21/2020

Expiration Date: 10/21/2023

The above referenced study has been *acknowledged*.

Review Type:	Exempt
Funding Agency:	Not funded
Grant or Contract Number:	
International Sites:	No
Maximum number of participants:	50
Vulnerable populations:	None
Consent process:	Survey/questionnaire consent
Assent Process:	

No changes may be made to the protocol or the consent form without the approval of the Board.

To keep the Homewood IRB files current, we are assigning an expiration date to projects that qualify as not human subjects research or exempt. You will receive an email notification prior to the expiration date shown above, providing guidance to extend this project.

Please keep this message in your files for future reference. Thank you for contacting the Homewood IRB about this research and for providing the requested information to make this determination. Your cooperation is greatly appreciated.

Please keep in mind that it is your responsibility to inform the HIRB of any adverse consequences to participants that occur in the course of the study, as well as any complaints from participants regarding the research. In conducting this research, you are required to follow the requirements listed in the *HIRB Policies and Procedures Manual*.

Please submit a closure application when this is completed.

Approved Documents:

Recruiting Materials:

HIRB00011867 Email script.docx

Study Team Members:

Carolina Manchola-Orozco

APPROVAL IS GRANTED UNDER THE TERMS OF FWA00005834 FEDERAL-WIDE ASSURANCE OF COMPLIANCE WITH DHHS REGULATIONS FOR PROTECTION OF HUMAN RESEARCH SUBJECTS
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Appendix 5. Orlando Health Institutional Review Board Exemption



1414 Kuhl Ave.
Orlando, FL 32806
321.843.7000
orlandohealth.com

FWA # 00000384

DATE: October 19, 2020

TO: Naren Ramakrishna, MD PhD
FROM: Orlando Health IRB #1

PROJECT TITLE: [1662027-1] Clinical Research Stakeholders' Goals and Expectations
REFERENCE #: 20.175.10
SUBMISSION TYPE: New Project

ACTION: DETERMINATION OF EXEMPT STATUS
DECISION DATE: October 19, 2020

REVIEW CATEGORY: Exemption category #2

Thank you for your submission of New Project materials for this project. The Orlando Health IRB #1 has determined this project is EXEMPT FROM IRB REVIEW according to federal regulations.

The Orlando Health IRB #1 has approved the waiver of documentation of informed consent (signature requirements) under 45CFR 46.117(C) for this project.

Please note that any revision to materials that have been previously reviewed by the IRB must be reviewed by this office prior to initiation. Please use the appropriate revision forms for this procedure.

We will retain a copy of this correspondence within our records.

If you have any questions, please contact the IRB Office at (321) 841-5895. Please include your project title and reference number in all correspondence with this committee.

This letter has been electronically signed in accordance with all applicable regulations, and a copy is retained within Orlando Health IRB #1's records.

Appendix 6. Brief Biography of the Author

Carolina Manchola-Orozco is a Society of Clinical Research Associates-certified Clinical Research Coordinator for neuro-oncology and radiation oncology at the Orlando Health Cancer Institute in Orlando, Florida. She has been conducting clinical research in adult oncology for the past five years and had previously coordinated pediatric optometry & ophthalmology clinical research for nearly three years at Bascom Palmer Eye Institute in Miami, Florida. She obtained her bachelor's degree at the University of Miami in psychology with a minor in Italian language, and first developed an interest in clinical research as a supervisor at the National Cancer Institute's Cancer Information Service. She enjoys spending time with her husband, daughter, and senior pug.